Review Article

Protective Role of *Hypericum perforatum* L. and*Hypericum triquetrifolium*Turra Against Inflammatory Diseases: Evidence from In Vitro and In Vivo Studies

ABSTRACT

More than 500 species of Hypericum are located throughout Europe, North America, North Africa, and Asia. These plants have a long history of employment in folk medicine as anti-inflammatory, antibacterial, and antiviral medicines, as well as for the treatment of burns, gastrointestinal problems, and depression. The most significant species of this genus are *Hypericum perforatum* L. and *Hypericum triquetrifolium*Turra because of their pharmacological activities. *Hypericum perforatum* L. and *Hypericum triquetrifolium* are widely known for their efficacy in reducing inflammation and improving wound healing. The main reason these plants have been used for treatment of mild to moderate depression. Nevertheless, some similar species are also utilized in conventional medicine and have been previously analyzed for their biological activity and phytochemical composition. The main classes of active substances are found in Hypericum species, including naphthodianthrones (such as hypericin and pseudohyperricin), phloroglucinols (such as hyperforin), flavonoids (such as rutin, hyperoside, isoquercitrin, quercitrin, and amentoflavone), and phenylpropanoids (chlorogenic acid). This review's objective is to provide a summary of the most recent research on potential medicinal uses for *Hypericum perforatum* L., and *Hypericum triquetrifolium*Turra

Keywords:*Hypericum triquetrifolium; Hypericum triquetrifolium; biological activities; inflammatory signaling; antioxidant.*

1. INTRODUCTION

There are approximately 500 plant species in the genus Hypericum, which belongs to the Hypericaceae family. These plants, five-petalled and yellow-flowered perennial weed, are most widely distributed in the moderate regions of Europe, North America, North Africa and Asia. Due to their broad spectrum of activity, numerous studies have been conducted around the world on the active ingredients of this genus. There have been claims made about the antibacterial, depressive, antiviral, anti-inflammatory, and antioxidant effects of various Hypericum species' extracts [1]. The best known Hypericum species are *Hypericum triquetrifolium*Turra (*H. triquetrifolium*) also known curled-leaved St. John's-wort (Fig. 1) and *Hypericum perforatum* L. (*H. perforatum*), also known St. John's wort and (Fig. 2) which are known for the antidepressant properties of their purified extracts. Eastern Europe and the Mediterranean are the native habitats of *H. perforatum* and *H. triquetrifolium*. They are perennial herbs in the Hypericaceae family that grow up to 45 cm tall. *H. perforatum* and *H.*

triquetrifolium are related. Both plants are members of the Hypericaceae family and have a variety of biologically active ingredients. They are interesting because of the abundance of bioactive special compounds they contain. Phloroglucinol derivatives, meroterpenoids, naphthodianthrones, xanthones, phenols, flavonoids, and essential oils are examples of compounds with demonstrated biological activity [2]. Recent studies on hypericin, one of the principal active constituents of Hypericum, have shown that it can inhibit viral replication and act as an anticancer drug by inducing apoptosis. In addition, hypericin has been found to inhibit HIV by weakening the exterior of the virus. Likewise, hypericin is essential for the elimination of food contaminating bacteria such as Listeria and Salmonella species and has photodynamic activity [3]. The potential of *H. perforatum* formulations for the treatment of dermatological conditions of current interest is being investigated. This traditional medicinal plant may be beneficial for treating skin diseases including psoriasis, viral infections, contact dermatitis, and white skin cancer. These compounds are also associated with anti-inflammatory, antimicrobial, and anticancer mechanisms, as well as stimulating tissue growth and differentiation. Hypericum oil, extracted from the flowering aerial parts of the plant or the fresh or dried flowers, is the most popular topical remedy [4,5].

Traditional Greco-Arabic herbal remedies that included *H. triquetrifolium* were employed to cure inflammatory conditions. This plant's traditional Arabic name is Dathi or NabtatYohanna (Fig. 1). *H. triquetrifolium* has also attracted great scientific interest in the last decade because, *H. triquetrifolium* is a medicinal plant that has a wide range of therapeutic effects since it is abundant in a number of bioactive chemicals [6]. Although *H. triquetrifolium*and *H. perforatum*are closely related and share numerous active chemicals, the plants demonstrate significant phytochemical variation [8]. In general, more than one active phytochemical is not thought to be responsible for the pharmacological effects seen in therapeutic herbs. Most often, the synergistic or antagonistic interactions between an extract's numerous elements are what cause it to act. As a result, we investigated *H. triquetrifolium* holistically by examining the effects of the methanolic extract, which has a variety of biologically active ingredients and demonstrated high antioxidant activity in our group's earlier research [8-10]. Regrettably, Palestinian healers no longer employ this herb. This fact illustrates the gradual disappearance of key aspects of the Arabic heritage of herbal remedy [11,12].

2. PHYTOCHEMICAL COMPOSITION

Hypericum species contain a large number of secondary metabolites, including phloroglucinol derivatives, naphthodianthrones, xanthones, flavonoids and other phenolic elements, as well as terpenoids, which have been discovered so far in Hypericum species [13, 3]. Currently, 768 phytochemicals have been identified from different Hypericum species Based on their biological functions, 160 of them have been documented for their biological activities [3]. In addition to terpenoids, spirolactone derivatives, and phenylpropanoid compounds (66), phytochemicals include derivatives of hyperforin (140), sampsoniones (93), Rottler-type compounds (40), spirocyclic phloroglucinols (25), simple benzophenones (82), simple phloroglucinol derivatives (131), xanthones (139), dianthrone compounds (11), and flavonoids (32) [14].

Since being isolated and thoroughly examined, phytochemicals from different Hypericum species were revealed to have anti-inflammatory, antioxidant, antineoplastic, antimicrobial, hepatoprotective, neuroprotective, antiviral, antidepressant, antinociceptive, antioxidant, antiparasitic, antimalarial, hypoglycemic, lipid-Lowering, and photodynamic activities. Table 1 lists the biological functions of Hypericum derivatives on inflammation and antioxidant effectiveness [3].

Table 1: Anti-inflammatory and antioxidant activities of bioactive phytochemical derivatives from Hypericum species [3].

Compound name	Phytochemical group	Hypericum Species	Anti-inflammatory and antioxidant activities
Norhypersampsone A	Benzophenones	*H. sampsonii*	Reduces NO release in LPS-induced RAW 264.7 macrophages
Monogxanthone A	Xanthone	*H. monogynum*	Reduces NO release in LPS-induced BV2 microglia cells
Monogxanthone B	Xanthone	*H. monogynum*	Inhibition of NO release in LPS-induced BV2 microglia cells
Hypermongone G	Hyperforin	*H. monogynum*	Reduces NO release
Cariphenone A	Benzophenones	*H. carinatum*	Antioxidant activity
5,7-Dihydroxy-2-isobutyl-4Hchromen-4-one	Flavonoids	*H. petiolulatum*	Antioxidant activity
Isoquercetin	Flavonoids	*H. thasium*	Protection against damage from H2O2-induced toxicity in H9C2 cells
Hyperoside	Flavonoids	*H. ascyron*	Protection against damage from H2O2-induced toxicity in H9C2 cells
Isohyperoside	Flavonoids	*H. ascyron*	Protection against damage from H2O2-induced toxicity in H9C2 cells
Hyperinakin	Benzophenones	*H. nakamurai*	anti-inflammatory activity
Otogirin	Phloroglucinol	*H. erectum*	Inhibitory production of thromboxane A2 and leukotriene D4
Otogirone	Phloroglucinol	*H. erectum*	1. Inhibitory production of thromboxane A2 and leukotriene D4

Hyperibrin A	Hyperforin	*H. scabrum*	Hepatoprotective effects
Hyperscabrone I	Hyperforin	*H. scabrum*	Hepatoprotective activity
Hyperscabrone C	Hyperforin	*H. scabrum*	Hepatoprotective activity
Hyperscabrone D	Hyperforin	*H. scabrum*	Hepatoprotective activity
Hyperscabrone D	Hyperforin	*H. scabrum*	Hepatoprotective activity
Hyperscabrone E	Hyperforin	*H. scabrum*	Hepatoprotective activity
Scrobiculatone B	Hyperforin	*H. scabrum*	Hepatoprotective activity
Hyperscabrone G	Hyperforin	*H. scabrum*	Hepatoprotective activity
Hyperibrin A	Hyperforin	*H. scabrum*	Neuroprotective activity
Hyperscabrone D	Hyperforin	*H. scabrum*	Neuroprotective activity
Hyperscabrone D	Hyperforin	*H. scabrum*	Neuroprotective activity
Hyperscabrone E	Hyperforin	*H. scabrum*	Neuroprotective effects
Hyperscabrone F	Hyperforin	*H. scabrum*	Neuroprotective activity
Hyperscabrone G	Hyperforin	*H. scabrum*	Neuroprotective activity
Hyperascyrin A	Hyperforin	*H. ascyron*	Neuroprotective efficacy against glutamate-induced toxicity in SK-N-SH cells
Hyperascyrin H	Hyperforin	*H. ascyron*	Neuroprotective efficacy against glutamate-induced toxicity in SK-N-SH cells
Monogxanthone A	Xanthone	*H. monogynum*	Neuroprotective efficacy in corticosterone in PC12 cells
Monogxanthone B	Xanthone	*H. monogynum*	Neuroprotective efficacy in corticosterone in PC12 cells
Hyperfoliatin	Hyperforin	*H. perfoliatum*	Reduce absorption of neuronal monoamine

Hyperforin	Hyperforin	*H. perforatum*	Antidepressant action in rats
Adhyperforin	Hyperforin	*H. perforatum*	Antidepressant action in mice
Hyperfoliatin	Hyperforin	*H. perfoliatum*	Antidepressant action in mice
Hyperbrasilol B	Rottlerin-type	*H. laricifolium*	Antidepressant action in mice
Andinin A	Rottlerin-type	*H. andinum*	Antidepressant action in mice
Uliginosin A	Rottlerin-type	*H. thesiifolium*	Antidepressant action in mice
Uliginosin B	Rottlerin-type	*H. uliginosum*	Antidepressant action in mice
Hypericin	Dianthrones	*H. perforatum*	Antidepressant action in mice
Uliginosin A	Rottlerin-type	*H. thesiifolium*	Antinociceptive action in mice
Uliginosin B	Rottlerin-type	*H. uliginosum*	Antinociceptive action in mice
Austrobrasilol A	Rottlerin-type	*H. austrobrasiliense*	Antinociceptive action in mice
Austrobrasilol B	Rottlerin-type	*H. austrobrasiliense*	Antinociceptive action in mice
Isoaustrobrasilol B	Rottlerin-type	*H. austrobrasiliense*	Antinociceptive action in mice
Japonicines A	Rottlerin-type	*H. polyanthemum*	Antinociceptive sensitivity in mice
6-Isobutyryl-5,7-dimethoxy-2,2-dimethyl-benzopyran	Phloroglucinol	*H. polyanthemum*	Antinociceptive sensitivity in mice

Hypericin, flavonoids, phenolic components such chlorogenic acid, and essential oil are all reported to be available in *H. triquetrifolium*, according to the published studies [15-17]. In previous research on the essential oil of H. triquetrifolium from Italy [18], the main components of the oil were identified as N-nonane 15%, germacrene-D 13%, caryophyllene oxide 12%, b-caryophyllene 11%, a-pinene 10%, myrcene 5%, b-pinene 4%, and sabinene 3%. One-hexanal 19%, 3-methylnonane 13%, -pinene 12%, caryophyllene oxide 5%, 2-methyldecane 5%, and -amorphene 4% are the major constituents of the essential oil extracted from the aerial portions of H. triquetrifolium cultivated in Turkey. Humulene, cis-calamenene, cadinene, bi-cyclogermacrene, eremophilene, caryo-phyllene, E-y-bisabolene, and pinene were also found to be the main constituents of the H. triquetrifolium oil from Tunisia. [19, 20].

3.1Biological Activities of*H. triquetrifolium*

Various studies have been done on this plant's antioxidant, antibacterial, anti-inflammatory, antinociceptive, and cytotoxic properties [21-25]. Four substances, specifically 3,8 biflavonoid, flavonol, flavonol glycoside, and phenolic acid "From the aerial portions of *H. triquetrifolium*'s ethyl acetate extract, biapigenin, quercetin, rutin, and chlorogenic acid were described. The analysis of the separated compounds' antioxidant activity revealed that 3,8 "Rutin, quercetin, and chlorogenic acid had slightly weaker activity than a-tocopherol

whereas biapigenin had similar activity to that of a-tocopherol [26]. The antioxidant effects of an ethanol extract of the species *H. triquetrifolium* have been further studied. The extract had a very high IC50 of 39.0 g/ml using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test. This suggests that the plant's ethanol extracts may be a source of organic antioxidants [27].

Due to their function in preserving the antioxidant system and delaying aging, atherosclerosis, and inflammatory disorders, potential novel antioxidant therapies are considered to be of high interest [28]. The most crucial element in the antidepressant action of Hypericum extracts is the inhibition of monoamine oxidase activity by the bioactive components of hypericin [29]. Only a few Hypericum species, such as *H. triquetrifolium* and *H. perforatum*, possess hypericin [15]. The medicinal plants' numerous biological functions, which have been documented in the literature, make them an intriguing source of medicine.

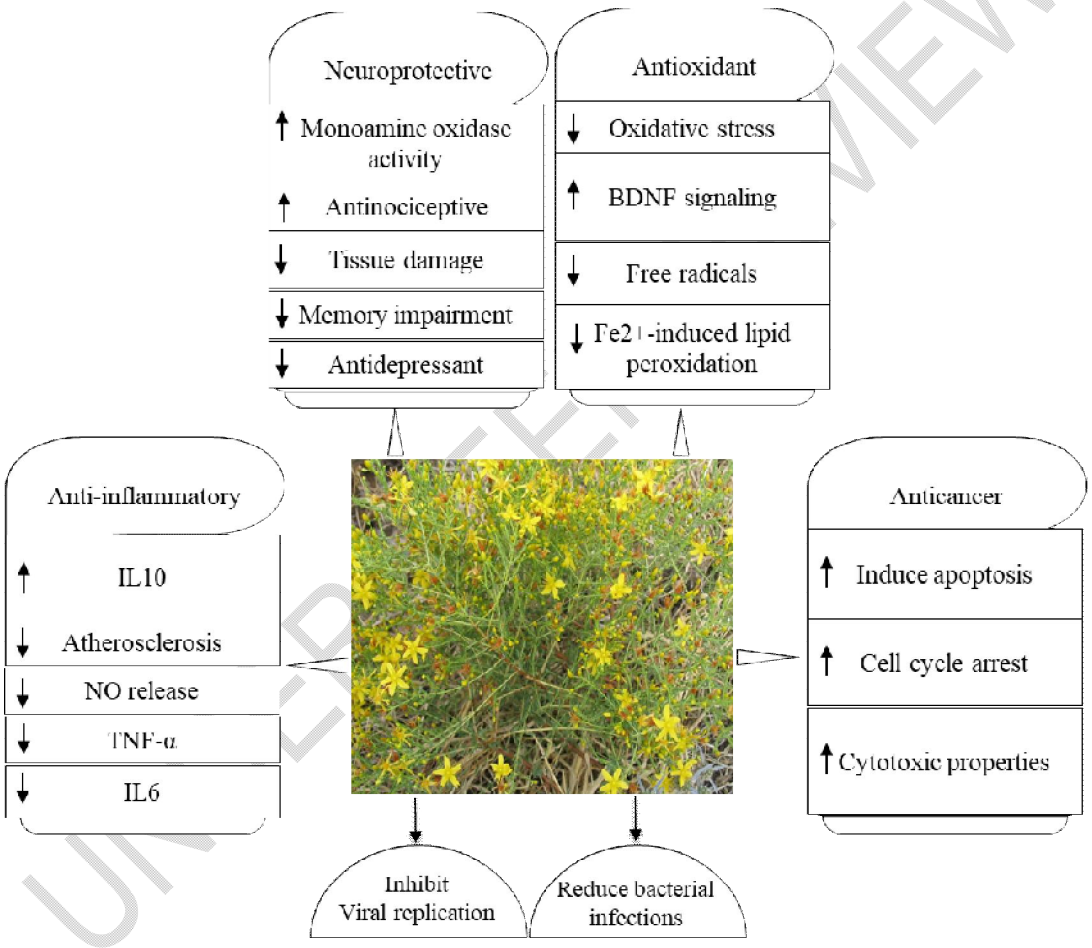

Figure 1. Biological activities of *Hypericum triquetrifolium*

3.2Anti-Inflammatory Effects of*H. triquetrifolium*

Inflammation is a sophisticated physiological reaction to pathogens or tissue damage that strives to get rid of the invader and get the system to its normal state [30]. It is acknowledged as a protective host response that is crucial for life but that, if dysregulated, can also be harmful. To keep tissue integrity, inflammation must be effectively controlled. Lack of control

over this defensive mechanism and the "misinterpretation" or persistence of inflammatory signals not only raise the risk of complex and widespread diseases like type 2 diabetes but also chronic inflammatory diseases like arthritis and autoimmune diseases [31–34].

Recent *in vivo* and *in vitro* investigations, as well as Greco-Arabic and Islamic medicine, all attest to the anti-inflammatory effects of *H. triquetrifolium* extract [35]. In human monocyte cell line (THP-1) cells, we examined the anti-inflammatory mechanism of *H. triquetrifolium*. The pro-inflammatory cytokines tumor necrosis factor (TNF-α), interleukin 6 (IL-6), and inducible nitric oxide synthase (iNOS) were all assessed for expression and release. *H. triquetrifolium* reduced NO and TNF-α production as well as iNOS and TNF-αgene expression, but not IL-6 [36, 37].

The anti-inflammatory impacts of *H. triquetrifolium* extracts (HT-extract) on lipopolysaccharide-stimulated human peripheral blood mononuclear cells (PBMNCs) were tested in another *in vitro* investigation [35]. By measuring the amounts of TNF-α, IL-, and interleukin 10 (IL-10) proteins and mRNA,

HT-extract doses up to 250 g/ml had no harmful effects when used in the anti-inflammatory impact experiments. At a concentration of 250 g/ml, HT-the extract dramatically reduced TNF-α and IL-6 expression and secretion. The extract considerably boosted the secretion of IL-10 and the levels of mRNA at a dosage of 125 g/ml of HT. Additionally, the DPPH assay revealed that the HT extract had reasonably strong antioxidant activity (IC50 of 5 g/ml). These findings imply that the HT-extract likely inhibits the expression of both pro- and anti-inflammatory cytokines at the protein and gene levels in PBMNCs [36–38].

An additional *in vivo* investigation examined the anti-inflammatory properties of *H. triquetrifolium* in a rat model of inflammation induced on by carrageenan. Thirty minutes before receiving a carrageenan injection, male Wistar rats were given intraperitoneal treatments of dimethyl sulfoxide (DMSO) (as a control group) and *H. triquetrifolium* extract. In contrast to saline injection, intraplantar carrageenan administration resulted in time-dependent paw edema in rats. Two hours after carrageenan injection, *H. triquetrifolium* extract (25, 50, or 60 mg/kg) was administered intraperitoneally and suppressed paw swelling in a dose-dependent manner, indicating that the extract may have anti-inflammatory effects in rats [38,39].

Another *in vitro* experiment looked into the effects of *H. triquetrifolium* extract (50% ethanol, 50% water) on apoptosis, cell cycle modulation, and cell cycle arrest in human colon cancer cell line (HCT-116) [40]. An Annexin V-Cy3 assay was used to determine if *H. triquetrifolium* extract caused cell death through the apoptotic mechanism. After being exposed to 0.064, 0.125, 0.25, and 0.5 mg/mL *H. triquetrifolium* extract for 24 hours, the percentage of apoptotic HCT-116 cells was 50.9%, 71.6%, 85.5%, and 96.1%, respectively. When HCT-116 cells were exposed to 0.25 and 0.5 mg/mL *H. triquetrifolium* extract for three hours, the amount of caspase-3-specific substrate that was cleaved was 38.9 1.5% and 57.2 3%, respectively. *H. triquetrifolium* extract showed no impact on the mRNA levels of Apaf-1 and NOXA, according to RT-PCR analysis. Furthermore, it was shown that adding 0.125 mg/mL and 0.25 mg/mL *H. triquetrifolium* extract for 24 hours slowed down the HCT-116 cells' ability to move through the cell cycle. The extract's GC/MS analysis revealed 21 phytochemicals that are known to promote apoptosis and function as cell cycle arrestant. The chemicals found in *H. triquetrifolium* are all brand-new. These findings imply that the caspase-dependent pathway plays a major role in the apoptosis that *H. triquetrifolium* extract causes in human colon cells. In light of this, *H. triquetrifolium* extract seems to be a potent therapeutic agent for the treatment of colon cancer [40].

Free radicals are atoms, molecules, or ions with unpaired electrons capable of independent existence that are formed by the internal natural metabolism of aerobic cells. Reactive free radicals include, for example, reactive oxygen species (ROS) and reactive nitrogen species (RNS). These species are created by inflammatory reactions, phagocytosis, the arachidonate pathway, ischemia, exercise, and metabolic reactions in mitochondria or peroxisomes [41–44]. Low concentrations of reactive species can alter the activity of

transcription factors like Nuclear factor-kappa B (NF-kappa B), Tumor protein P53, and Nuclear factor erythroid 2-related factor 2 (NRF2) and set off a number of protein kinase cascades that regulate how autophagy, apoptosis, and regeneration interact.
However, under physiological circumstances, the production of reactive species can be balanced by internal and external forms of antioxidants. Endogenous antioxidant defense can be either non-enzymatic (such as uric acid, glutathione, bilirubin, thiols, albumin, and dietary components including vitamins and phenols) or enzymatic (such as glutathione peroxidase, catalase, and superoxide dismutase) [45, 46]. Numerous investigations have demonstrated that different Hypericum species are important sources of free radical scavengers, metal chelators, and lipid peroxidation inhibitors.
DPPH, metal chelating, reducing power, hydroxyl radical, total antioxidant activity, and lipid peroxidation inhibition tests, the antioxidant activity of ethanol extracts of *H. triquetrifolium* and *H. scabroides* was examined [47]. The DPPH radical scavenging assay revealed that both of the studied extracts were quite effective. In the DPPH radical scavenging assay, the IC50 values of *H. triquetrifolium* and *H. scabroides* were 39.0 and 33.8 g/ml, respectively. The total phenolic compound content was also identified, and it was shown that 1 mg of the ethanol extracts of *H. triquetrifolium* and *H. scabroides* had total phenolic contents that were equivalent to 267 and 333 g of gallic acid, respectively. The ability to chelate metals was found to be less effective than EDTA. High reducing power was demonstrated by both Hypericum species' ethanol extracts, spiculate that the extracts possess strong electron donor ability. Hypericum extracts were proven to restrict the hydroxyl radical's ability to break down deoxyribose, mostly via scavenging hydroxyl radicals as compared to chelating iron ions. Ferric thiocyanate (FTC) and thiobarbituric acid (TBA) techniques were used to assess the overall antioxidant activity of ethanol extracts from *H. triquetrifolium* and *H. scabroides*. Both extracts had antioxidant activity that was comparable to vitamin E. Furthermore, in rat brain homogenate, both extracts displayed an extraordinary capacity to inhibit Fe2+-induced lipid peroxidation. These findings imply that extracts of *H. triquetrifolium* and *H scabroides* may be a source of free radicals in nature [48].

4. PROTECTIVE ROLE AND THERAPEUTIC EFFECTS OF *H. perforatum*

One of the most extensively examined medicinal plants is *H. perforatum*(Fig. 2), it is likely the most well-known one available today. The ancient Greeks were the first to use this species as an herbal cure to heal a wide range of internal and exterior illnesses. Since then, it has continued to be a well-liked treatment for burns, depression, and anxiety. It is also employed as a plant that is antiviral, antineuralgic, and neuroprotective [48]. Recent studies have shown the effectiveness of *H. perforatum* in the management of a wide range of complications, such as cancer, inflammation-related illnesses, diabetes, bacterial and viral illnesses, as well as an antioxidant and neuroprotective agent [48, 49].
Pharmaceutical drugs made from *H. perforatum* currently, consumed by millions of people, generate annual sales of over a few billion dollars worldwide. As was already noted, *H. perforatum* has a large number of active ingredients. Hypericin and hyperforin are thought to be responsible for a large portion of *H. perforatum*'s medicinal properties. Other substances also seem to have therapeutic potential, such as the flavonoids rutin, quercetin, and kaempferol. In-depth research has been done on *H. perforatumin vitro*, *in vivo* on animal models, and in clinical trials. This plant's ability to treat depression has been extensively researched, and the underlying mechanisms are well understood. When consumed at recommended doses, products from *H. perforatum* have comparatively low negative effects. Nevertheless, several drug interactions have been documented. Recent research suggests that these interactions are caused by the components of *H. perforatum*'s capacity to stimulate the hepatic or intestinal cytochrome P450 enzymes [47, 48]. *In vitro* and animal studies have shown that extracts of *H. perforatum* have significant anti-inflammatory activity. For example, rats fed *H. perforatum* had lower levels of blood and intestinal enzymes

responsible for inflammation of the colon [50] and showed a lower incidence of gastric ulceration [51]. *H. perforatum* hydrophobic extracts were even more potent anti-inflammatory agents than hydroalcoholic extracts [52]. The anti-inflammatory properties of *H. perforatum* have been attributed to three different modes of action. The expression of proinflammatory genes such cyclooxygenase-2, IL-6, and inducible iNOS was reduced by extracts of *H. perforatum* [53]. Extensive research with the latter approach shown that *H. perforatum*extracts reduced Janus kinase 2 activity, which in turn triggered a sequence of reactions that prevented the downregulation of STAT-1-DNA binding and further disturbed gene transcription [53]. Prostaglandin E2 (PGE2), a molecule associated with inflammation, was prevented from being produced by pseudohypericin and hyperforin [54]. Chloric acid, amentoflavone, quercetin, and pseudohypericin were shown to be the four main components of the *H. perforatum* extract that worked together to diminish the inflammation caused by PGE2 [55]. This four-part mechanism seems to have only been effective when pseudohypericin was activated in the light presence. In experimental mice that had pleurisy brought on by carrageenan, *H. perforatum* extract also decreased inflammation [55]. The extracts had several effects, most notably suppressing STAT -3 and NF-kappa B[56].

According to recent findings, *H. perforatum* extracts can prevent neurotoxicity, inflammation, and digestive issues by reducing oxidative stress. This herb's extracts that are high in flavonoids can prevent PC12 cells from going into apoptosis when exposed to hydrogen peroxide. As a result of hydrogen peroxide activity, *H. perforatum* extracts can stop DNA fragmentation and cell shrinkage [57]. Therefore, oxidative stress-related neurodegenerative illnesses including Parkinson's disease and Alzheimer's disease can be successfully treated with *H. perforatum* extracts rich in flavonoids [58].

By lowering mitochondrial lipid membrane oxidation and maintaining mitochondrial transmembrane electrical potential, quercetin and kaempferol have neuroprotective effects [59]. Contrarily, biapigenin mainly affects mitochondrial bioenergetics and reduces their capacity to take up calcium [59]. In addition, animals treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) showed lower astrocyte activation and MAO-B activity when *H. perforatum* extract was administered [60]. As a result, *H. perforatum* protects against Parkinson's disease in mice caused by MPTP [60]. By lowering mitochondrial lipid membrane oxidation and maintaining mitochondrial transmembrane electrical potential, quercetin and kaempferol have neuroprotective effects [59]. Contrarily, biapigenin mainly affects mitochondrial bioenergetics and reduces their capacity to take up calcium [59]. In addition, animals treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) showed lower astrocyte activation and MAO-B activity when *H. perforatum* extract was administered [60]. As a result, *H. perforatum* protects against Parkinson's disease in mice caused by MPTP [60].

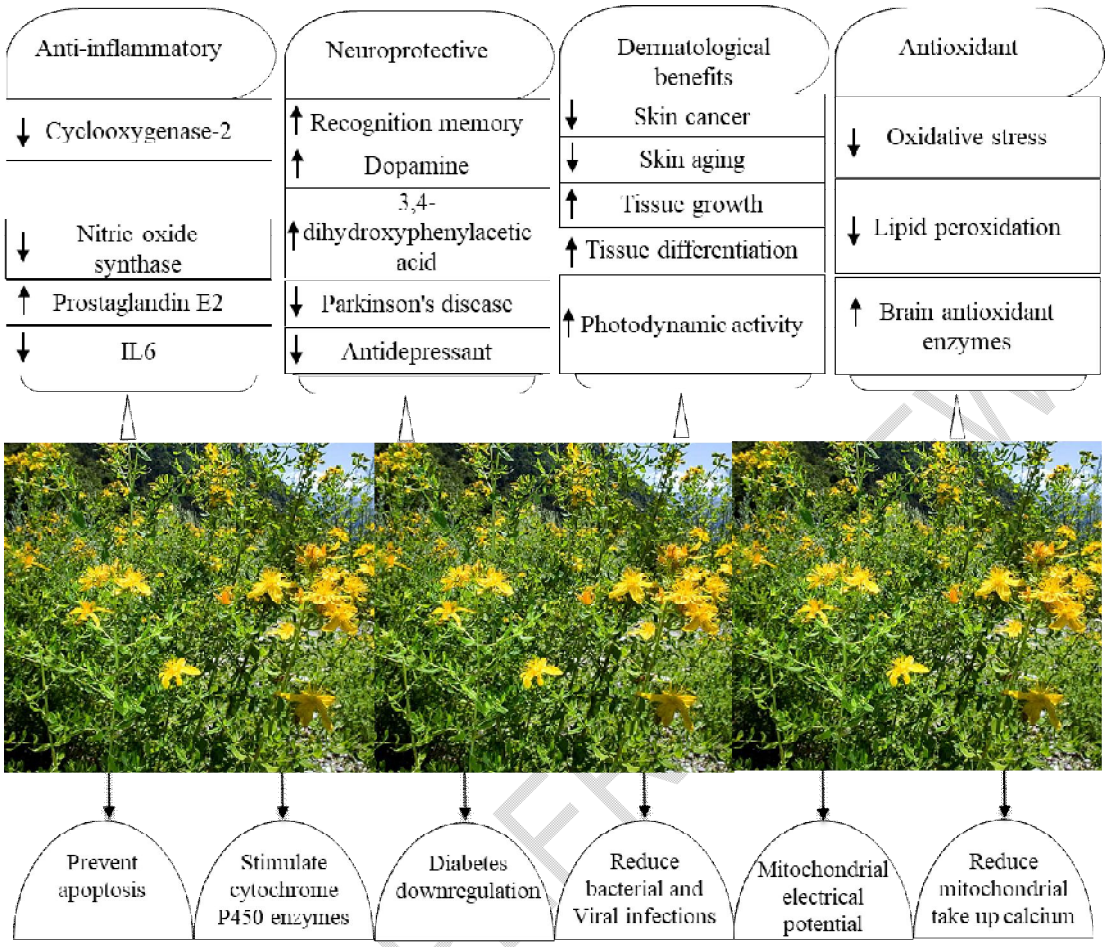

Figure 2. Biological activities of *Hypericum perforatum*

More research revealed that MPTP-induced Parkinson's disease in male Swiss albino mice may be treated with a combination of bromocriptine and *H. perforatum* extract that dramatically boosted dopamine and 3,4-dihydroxyphenylacetic acid, a metabolite of dopamine [61]. In cultured rat hippocampus neurons, ethanolic extracts of *H. perforatum* and those containing flavonol glycosides, flavonol, and biflavone aglycones reduced lipid peroxidation and cell death [62]. In microglia, flavonoids reduced the production of amyloid-induced reactive oxygen species. Microglia's cell survival and membrane fluidity were both boosted by the flavanols (+)-catechin and (-)-epicatechin from *H. perforatum* [63]. When given extracts from *H. perforatum*, rats subjected to chronic stress performed better in terms of working memory, recognition memory, and recollection of passive avoidance behaviors compared to control individuals who did not receive extracts [64]. The herb greatly enhanced spatial working memory that is hippocampus-dependent and mitigated the detrimental effects of stress on cognitive performance [64]. *H. perforatum* extracts decreased oxidative stress in the brains of rats given rotenone, a pro-oxidant [65]. These results were attributable to liposomal quercetin, which considerably preserved the antioxidant enzymes' functions in the brain tissue. It has been concluded that standardized extracts of *H. perforatum* may be the preferred treatment for depressed older individuals showing degenerative diseases linked with increased oxidative stress [65].

A preparation containing a hyperforin-rich extract of *H. perforatum* had an effect on free radical scavenging cells in a double-blind, placebo-controlled study in 11 healthy subjects [66]. The results suggest that application of the hyperforin-rich cream to the skin can prevent the production of radicals by more than 80%. A formulation free of hypericin and containing 44.3% hyperforin was tested for its ability to block free radicals and provide photoprotection *in vivo*. These results show that hyperforin is an effective free radical scavenger and that it can be used to reduce the degree of skin aging. To the best of the authors' knowledge, the antioxidant capacity of Hypericum species remains the most widely documented compared to other biological cosmeceutical tests [42, 67].

The researchers studied the antioxidant capacity and free radical scavenging ability of the constituents of *H. perforatum* plant. The test of reducing capacity of iron in plasma was used to determine the total antioxidant effect of the ethanolic extract. The ethanolic extract of *H. perforatum* was found to contain a significant number of total flavonoids. In addition, the ethanolic extract of *H. perforatum* showed strong antioxidant activity. Moreover, the ability of the ethanolic extract to scavenge flavonoids was time-dependent. The ethanolic extract of *H. perforatum* showed considerable free radical scavenging activity against ABTS. The ethanolic extracts of *H. perforatum* had a gradual but consistent level of dynamic DPPH and ABTS scavenging activity. The amount of total flavonoids or phenolic acids present could play an important role in the antioxidant activity and free radical scavenging activity [68]. A study conducted in Syria on the aerial parts of St. John's wort - leaves, stems, petals, and flowers -found that water, ethanol, methanol, and acetone extracts were all efficient scavengers of ABTS and DPPH stable free radicals. Extracts with a higher concentration of phenols were remarkably efficient radical scavengers [69, 70].

The antioxidant activities of the bioactive components in water-ethanol and water extracts of flowers, flower buds, flower-bearing branches, non-flower-bearing branches, and shoots with leaves of *H. perforatum* were investigated. The water-ethanol extract of shoots had the highest content of phenols, and the water-ethanol extract of flowers had the highest concentrations of hypericin and pseudohypericin. While *H. perforatum*flowers had the highest concentration of hyperforin throughout the development period, floral buds had the highest concentration. Additionally, because to their high phenolic content, branches and shoots demonstrated significant antioxidant activity [71, 72].

A verum cream with 1.5% of an *H. perforatum* extracts and hyperforin (44.3%) was investigated for its ability to scavenge free radicals when skin cells were subjected to solar-stimulated radiation. The extract of *H. perforatum* lacked hypericin. According to the results [72], hyperforin may be a potent free radical scavenger, as evidenced by the cream's antioxidative action and hyperforin-rich HP extract. The effectiveness of the verum cream on the barrier function and the radical skin protection offered by topically applying it during visible/near infrared (VIS/NIR) irradiation were evaluated in a placebo-controlled, double-blind trial. When a single application of basic cream without *H. perforatum* extract was performed, both the placebo and verum creams nearly completely inhibited the radical generation, and both creams also offered an immediate level of protection. Furthermore, after applying basic and verum creams for 4 weeks, the radical production was reduced by 45% and 78%, respectively [73].

5. HERBAL REMEDIES CONSIDERATION REMARKS

The detection and purification of specific immunomodulatory plant compounds has the potential to reduce the side effects and high cost of conventional drugs [74]. Both *H. perforatum*and *H. triquetrifolium*are popular mental treatment herbs. Therefore, psychological issues are the focus of the majority of treatment research conducted on these two species. However, numerous *in vitro*, *in vivo*, and clinical investigations have shown that it has promise medicinal effects for a variety of conditions, including inflammation, infectious issues, and skin disorders, which may someday replace standard medical therapies. The

range of medication interactions that *H. perforatum* and *H. triquetrifolium*can induce is one of its most significant characteristics. The findings of this study can serve as a guide for future research into the anti-inflammatory properties of similar compounds.

CONSENT (WHERE EVER APPLICABLE)

It is not applicable.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

It is not applicable.

REFERENCES

1. Zhao J, Liu W, Wang JC. Recent advances regarding constituents and bioactivities of plants from the genus Hypericum. Chem Biodivers. 2015;12(3):309-49. doi: 10.1002/cbdv.201300304. PMID: 25766907.
2. de Carvalho Meirelles G, Bridi H, von Poser GL, Nemitz MC. Hypericum species: An analysis on the patent technologies. Fitoterapia. 2019;139:104363. doi: 10.1016/j.fitote.2019.104363.
3. Xiao CY, Mu Q, Gibbons S. The Phytochemistry and Pharmacology of Hypericum. Prog Chem Org Nat Prod. 2020;112:85-182. doi: 10.1007/978-3-030-52966-6_2.
4. Wölfle U, Seelinger G, Schempp CM. Topical application of St. John's wort (Hypericum perforatum). Planta Med. 2014;80(2-3):109-20. doi: 10.1055/s-0033-1351019.
5. Silva AR, Taofiq Q, Isabel C.F.R. Ferreira, Lillian Barros. Hypericum genus cosmeceutical application- A decade comprehensive review on its multifunctional biological properties. Industrial Crops and Products. 2020;159,2021, 113053. https://doi.org/10.1016/j.indcrop.2020.113053.
6. Aleisa AM. Cytological and biochemical effects of St. John’s wort supplement (a complex mixture of St. John’s wort, Rosemary and Spirulina) on somatic and germ cells of Swiss Albino mice. Int J Environ Res Public Health. 2008;5(5):408–417. doi:10.3390/ijerph5050408.
7. Al-Eisawi DM. Field Guide to Wild Flowers of Jordan and Neighbouring Countries. Amman, Jordan: Jordan Press Founation, Al-Rai; 1998.
8. Nürk NM, Crockett SL. Morphological and Phytochemical Diversity among Hypericum Species of the Mediterranean Basin. Med Aromat Plant Sci Biotechnol. 2011;5(1):14-28. PMID: 22662020; PMCID: PMC3364718.
9. Alali FQ, Tawaha K, El-Elimat T, et al. Antioxidant activity and total phenolic content of aqueous and methanolic extracts of Jordanian plants: an ICBG project. Nat Prod Res. 2007;21(12):1121–1131. doi:10.1080/14786410701590285.
10. Tawaha K, Alali FQ, Gharaibeh M, Mohammad M, El-Elimat T. Antioxidant activity and total phenolic content of selected Jordanian plant species. Food Chem. 2007;104(4):1372–1378. doi:10.1016/j.foodchem.2007.01.064.
11. Saad B, Azaizeh H, Said O. Tradition and perspectives of arab herbal medicine: a review. Evid Based Complement Alternat Med. 2005;2(4):475-9. doi: 10.1093/ecam/neh133.
12. Saad B, Azaizeh H, Said O. Arab botanical medicines. The Encyclopedia of Botanicals in Clinical Practice edited by Profs. Ron Watson and Victor Preedy 2008.
13. Zhang R, Ji Y, Zhang X, Kennelly EJ, Long C. Ethnopharmacology of Hypericum species in China: A comprehensive review on ethnobotany, phytochemistry and

pharmacology. J Ethnopharmacol. 2020; 23;254:112686. doi: 10.1016/j.jep.2020.112686.
14. Cabrelle A, Dell'Aica I, Melchiori L, Carraro S, Brunetta E, Niero R, Scquizzato E, D'Intino G, Calzà L, Garbisa S, Agostini C. Hyperforin down-regulates effector function of activated T lymphocytes and shows efficacy against Th1-triggered CNS inflammatory-demyelinating disease. J Leukoc Biol. 2008;83(1):212-9. doi: 10.1189/jlb.0707469.
15. Alali F, Tawaha K, Al-Eleimat T. Determination of hypericin content in Hypericum triquetrifolium Turra (Hypericaceae) growing wild in Jordan. Nat Prod Res. 2004;18:147–151. [PubMed] [Google Scholar].
16. Cirak C, Radusiene J, Janulis V, Ivanauskas L, Camas N, Ayan AK. Phenolic constituents of Hypericum triquetrifolium Turra (Guttiferae) growing in Turkey: variation among populations and plant parts. Turk J Biol. 2011;35:449–456. [Google Scholar].
17. Hosni K, Msaada K, Ben-Taarit M, Marzouk B. Phenological variations of secondary metabolites from Hypericum triquetrifolium Turra. Biochem Syst Ecol. 2011;39:43–50. [Google Scholar].
18. Bertoli A, Menichini F, Mazzetti M, Spinelli G, Morelli I. Volatile constituents of the leaves and flowers of Hypericum triquetrifolium Turra. Flav Frag J. 2003;18:91–94. [Google Scholar].
19. Yuce E, Bagci E. The essential oils of the aerial parts of two Hypericum taxa (Hypericum triquetrifolium and Hypericum aviculariifolium subsp. depilatum var. depilatum (Clusiaceae) from Turkey. Nat Prod Res. 2011;26:1985–1990. [PubMed] [Google Scholar].
20. Karim H, Kamel M, Mouna BT, Thouraya C, Brahim M. Essential oil composition of Hypericum triquetrifolium Turra. aerial parts. Ital J Biochem. 2007;56:40–46. [PubMed] [Google Scholar].
21. Conforti F, Statti AG, Tundis R, Menichini F, Houghton P. Antioxidant activity of methanolic extract of Hypericum triquetrifolium Turra aerial part. Fitoterapia. 2002;73:479–483. [PubMed] [Google Scholar].
22. Kizil G, Toker Z, Ozen HC, Aytekin C. The antimicrobial activity of essential oils of Hypericum scabrum, Hypericum scabroides and Hypericum triquetrifolium. Phytother Res. 2004;18:339–341. [PubMed] [Google Scholar].
23. Ozturk B, Apaydin S, Goldeli E, Ince I, Zeybek U. Hypericum triquetrifolium Turra. Extract exhibits antiinflammatory activity in the rat. J Ethnopharmacol. 2002;80:207–209. [PubMed] [Google Scholar].
24. Apaydin S, Zeybek U, Ince I, Elgin G, Karamenderes C, Ozturk B, Tuglular I. Hypericum triquetrifolium Turra. extract exhibits antinociceptive activity in the mouse. J Ethnopharmacol. 1999;67:307–312. [PubMed] [Google Scholar].
25. Conforti F, Loizzo MR, Statti AG, Menichini F. Cytotoxic activity of antioxidant constituents from Hypericum triquetrifolium Turra. Nat Prod Res. 2007;21:42–46. [PubMed] [Google Scholar].
26. Couladis M, Baziou P, Verykokidou E, Loukis A. Antioxidant activity of polyphenols from Hypericum triquetrifolium Turra. Phytother Res. 2002;16:769–770. [PubMed] [Google Scholar].
27. Kizil G, Kizil M, Yavuz M, Emen S, Hakimoglu F. Antioxidant Activities of Ethanol Extracts of Hypericum triquetrifolium. And Hypericum scabroides. Pharm Biol. 2008;46:231–242. [Google Scholar].
28. Kang JH. Protection by carnosine and homocarnosine against L-DOPA-Fe(III)-mediated dna cleavage. Bull Korean Chem Soc. 2005;26:1251–1254. [Google Scholar].
29. Thiede HM, Walper A. Inhibition of MAO and COMT by Hypericum extracts and hypericin. J Geriatr Psychiatry Neurol. 1994;7:54–56. [PubMed] [Google Scholar].

30. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008 Jul 24;454(7203):428-35. doi: 10.1038/nature07201.
31. Cao H, Ou J, Chen L, Zhang Y, Szkudelski T, Delmas D, Daglia M, Xiao J. Dietary polyphenols and type 2 diabetes: Human Study and Clinical Trial. Crit Rev Food Sci Nutr. 2019;59(20):3371-3379. doi: 10.1080/10408398.2018.1492900.
32. Khan H, Sureda A, Belwal T, Çetinkaya S, Süntar İ, Tejada S, Devkota HP, Ullah H, Aschner M. Polyphenols in the treatment of autoimmune diseases. Autoimmun Rev. 2019 Jul;18(7):647-657. doi: 10.1016/j.autrev.2019.05.001.
33. Jin T, Song Z, Weng J, Fantus IG. Curcumin and other dietary polyphenols: potential mechanisms of metabolic actions and therapy for diabetes and obesity. Am J Physiol Endocrinol Metab. 2018 Mar 1;314(3):E201-E205. doi: 10.1152/ajpendo.00285.2017. Epub 2017 Oct 31.
34. Saad B, Dakwar S, Said O, Abu Hijleh G, Albattah F, Kmeel AS, et al. Evaluation of medicinalplants hepatotoxicity using co-cultures of hepatocytes and monocytes. EvidBasedComplementAlternat Med 2006; 3:93–8.
35. Saad B, Said O. Herbal Medicine. In Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy and Regulatory Issues. Wiley-Blackwell John Wiley & Sons, Inc. 2011;149-227.
36. Saad B, Embaslat W, Abu Farich B, MahajnaSh, Azab M, Daragmeh J, Khasib S, Zaid H. Hypericum Triquetrifolium –extracts modulate IL-6, IL-10 and TNF-α protein and mRNA expression in LPS-activated human peripheral blood mononuclear cells and THP-1-derived macrophages, Medicinal & Aromatic Plants. 2016;4(4):1-6. doi:10.4172/2167-0412.S3-004.
37. Saad B, Abouatta BS, Basha W, Hmade A, Kmail A, Khasib S, Said O. Hypericum triquetrifolium-Derived Factors Downregulate the Production Levels of LPS-Induced Nitric Oxide and Tumor Necrosis Factor-α in THP-1 Cells. Evid Based Complement Alternat Med. 2011;2011:586470. doi: 10.1093/ecam/nen056. Epub 2011 Feb 20.
38. Saad B, AbouAtta SB, Basha W, Kmeel AS, Khasib S, Hmade A, Said O. Herbal-derived factors down regulate the production levels of nitric oxide and pro-inflammatory cytokine TNF-□ in LPS-Activated THP-1 cells. Evid Based Complement Alternat Med. 2008. doi:10.1093/ecam/nen056.
39. Kızıl G, Kızıl M, Yavuz M, Emen S, Hakimoglu F. Antioxidant Activities of Ethanol Extracts of Hypericum triquetrifolium and Hypericum scabroides. Pharmaceutical Biology. 2008;46:4, 231-242, DOI: 10.1080/13880200701739363.
40. Mahajna S, Kadan S, Tietel Z, Saad B, Khasib S, Tumeh A, Ginsberg D, Zaid H. In vitro Assessment of Apoptosis Induction and Cell Colon Cancer Cell Line by Chemically Analyzed Hypericum triquetrifolium Extract. Molecules. 2019;24:4139. doi: 10.3390/molecules24224139.
41. Barros L, Morales P, Carvalho AM, Ferreira ICFR. 2016. Antioxidant potential of wild plant foods. Mediterranean Wild Edible Plants: Ethnobotany and Food Composition Tables. Springer, New York. 2016;209–232. https://doi.org/10.1007/ 978-1-4939-3329-7_10.
42. Silva AR, Taofiq Q, Isabel C.F.R. Barros FL.Hypericum genus cosmeceutical application – A decade comprehensive review on its multifunctional biological properties. Industrial Crops and Products,2021;159:113053,https://doi.org/10.1016/j.indcrop.2020.113053.
43. Carocho M, Ferreira I.C.F.R. 2013. A review on antioxidants, prooxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives. Food Chem. Toxicol. 2012;51:15–25. https://doi. org/10.1016/j.fct.2012.09.021.
44. Ferreira I, Barros L, Abreu R. Antioxidants in wild mushrooms. Curr. Med. Chem. 2009;16:1543–1560. https://doi.org/10.2174/092986709787909587.

45. Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. Dermatoendocrinol. 2012;4:308–319. https://doi.org/ 10.4161/derm.22804.
46. Sharma AK, Taneja G, Khanna D, Rajput SK. Reactive oxygen species: friend or foe? RSC Adv. 2015;5:57267–57276. https://doi.org/10.1039/c5ra07927f.
47. Kızıl G, Kızıl M, Yavuz M, Emen S, Hakimoğlu F. Antioxidant Activities of Ethanol Extracts of Hypericum triquetrifolium. and Hypericum scabroides. Pharmaceutical Biology. 2008;46(4):231-42.https://doi.org/10.1080/13880200701739363.
48. Nobakht SZ, Akaberi M, Mohammadpour AH, Tafazoli Moghadam A, Emami SA. Hypericum perforatum: Traditional uses, clinical trials, and drug interactions. Iran J Basic Med Sci. 2022 Sep;25(9):1045-1058. doi: 10.22038/IJBMS.2022.65112.14338.
49. Klemow KM, Bartlow A, Crawford J, Kocher N, Shah J, Ritsick M. Medical Attributes of St. John's Wort (Hypericum perforatum). In: Benzie IFF, Wachtel-Galor S, editors. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2011. Chapter 11. PMID: 22593920.
50. Dost T, Ozkayran H, Gokalp F, Yenisey C, Birincioglu M. The effect of Hypericum perforatum (St. John's Wort) on experimental colitis in rat. Dig Dis Sci. 2009 Jun;54(6):1214-21. doi: 10.1007/s10620-008-0477-6. Epub 2008 Aug 27.
51. Cayci MK, Dayioglu H. Hypericum perforatum extracts healed gastric lesions induced by hypothermic restraint stress in Wistar rats. Saudi Med J. 2009 Jun;30(6):750-4. PMID: 19526154.
52. Sosa S, Pace R, Bornancin A, Morazzoni P, Riva A, Tubaro A, Della Loggia R. Topical anti-inflammatory activity of extracts and compounds from Hypericum perforatum L. J Pharm Pharmacol. 2007 May;59(5):703-9. doi: 10.1211/jpp.59.5.0011.
53. Tedeschi E, Menegazzi M, Margotto D, Suzuki H, Förstermann U, Kleinert H. Anti-inflammatory actions of St. John's wort: inhibition of human inducible nitric-oxide synthase expression by down-regulating signal transducer and activator of transcription-1alpha (STAT-1alpha) activation. J Pharmacol Exp Ther. 2003 Oct;307(1):254-61. doi: 10.1124/jpet.103.054460.
54. Hammer KD, Hillwig ML, Solco AK, Dixon PM, Delate K, Murphy PA, Wurtele ES, Birt DF. Inhibition of prostaglandin E(2) production by anti-inflammatory hypericum perforatum extracts and constituents in RAW264.7 Mouse Macrophage Cells. J Agric Food Chem. 2007 Sep 5;55(18):7323-31. doi: 10.1021/jf0710074. Epub 2007 Aug 15.
55. Hammer KD, Hillwig ML, Neighbors JD, Sim YJ, Kohut ML, Wiemer DF, Wurtele ES, Birt DF. Pseudohypericin is necessary for the light-activated inhibition of prostaglandin E2 pathways by a 4 component system mimicking an Hypericum perforatum fraction. Phytochemistry. 2008 Sep;69(12):2354-62. doi: 10.1016/j.phytochem.2008.06.010. Epub 2008 Aug 15.
56. Menegazzi M, Di Paola R, Mazzon E, Muià C, Genovese T, Crisafulli C, Suzuki H, Cuzzocrea S. Hypericum perforatum attenuates the development of carrageenan-induced lung injury in mice. Free Radic Biol Med. 2006 Mar 1;40(5):740-53. doi: 10.1016/j.freeradbiomed.2005.08.034. Epub 2005 Nov 10.
57. Lu YH, Du CB, Liu JW, Hong W, Wei DZ. Neuroprotective effects of Hypericum perforatum on trauma induced by hydrogen peroxide in PC12 cells. Am J Chin Med. 2004;32(3):397-405. doi: 10.1142/S0192415X04002053.
58. Zou YP, Lu YH, Wei DZ. Protective effects of a flavonoid-rich extract of Hypericum perforatum L. against hydrogen peroxide-induced apoptosis in PC12 cells. Phytother Res. 2010 Jan;24 Suppl 1:S6-S10. doi: 10.1002/ptr.2852.

59. Silva B, Oliveira PJ, Dias A, Malva JO. Quercetin, kaempferol and biapigenin from Hypericum perforatum are neuroprotective against excitotoxic insults. Neurotox Res. 2008 May-Jun;13(3-4):265-79. doi: 10.1007/BF03033510.
60. Mohanasundari M, Sabesan M. Modulating effect of Hypericum perforatum extract on astrocytes in MPTP induced Parkinson's disease in mice. Eur Rev Med Pharmacol Sci. 2007 Jan-Feb;11(1):17-20. PMID: 17405345.
61. Mohanasundari M, Srinivasan MS, Sethupathy S, Sabesan M. Enhanced neuroprotective effect by combination of bromocriptine and Hypericum perforatum extract against MPTP-induced neurotoxicity in mice. J Neurol Sci. 2006 Nov 15;249(2):140-4. doi: 10.1016/j.jns.2006.06.018. Epub 2006 Jul 31.
62. Silva BA, Dias AC, Ferreres F, Malva JO, Oliveira CR. Neuroprotective effect of H. perforatum extracts on beta-amyloid-induced neurotoxicity. Neurotox Res. 2004;6(2):119-30. doi: 10.1007/BF03033214.
63. Kraus B, Wolff H, Heilmann J, Elstner EF. Influence of Hypericum perforatum extract and its single compounds on amyloid-beta mediated toxicity in microglial cells. Life Sci. 2007 Aug 23;81(11):884-94. doi: 10.1016/j.lfs.2007.07.020.
64. Trofimiuk E, Braszko JJ. Alleviation by Hypericum perforatum of the stress-induced impairment of spatial working memory in rats. NaunynSchmiedebergs Arch Pharmacol. 2008 Feb;376(6):463-71. doi: 10.1007/s00210-007-0236-9. Epub 2007 Dec 19.
65. Sánchez-Reus MI, Gómez del Rio MA, Iglesias I, Elorza M, Slowing K, Benedí J. Standardized Hypericum perforatum reduces oxidative stress and increases gene expression of antioxidant enzymes on rotenone-exposed rats. Neuropharmacology. 2007 Feb;52(2):606-16. doi: 10.1016/j.neuropharm.2006.09.003.
66. Arndt S, Haag SF, Kleemann A, Lademann J, Meinke MC. Radical protection in the visible and infrared by a hyperforin-rich cream - in vivo versus ex vivo methods. Exp. Dermatol. 2013;22:354–357. https://doi.org/10.1111/exd.12124.
67. Meinke MC, Schanzer S, Haag SF, Casetti F, Müller ML, Wolfle U, Kleemann A, Lademann J, Schempp CM. In vivo photoprotective and anti-inflammatory effect of hyperforin is associated with high antioxidant activity in vitro and ex vivo. Eur. J. Pharm. Biopharm. 2012;81:346–350. https://doi.org/10.1016/j. ejpb.2012.03.002.
68. Li Y, Liu Y, Xiao B, Tang J, Huang R. Dynamic comparison of free radical scavenging abilities of Hypericum perforatum L., HerbaVerbenae officinalis, and Valeriana officinalis L. extracts. Phcog J. 2015;7(3):198-204.DOI:10.5530/pj.2015.3.9.
69. Alahmad A, Alghoraibi I, Zein R, Kraft S, Dräger G, Walter JG, Scheper T. Identification of Major Constituents of Hypericum perforatum L. Extracts in Syria by Development of a Rapid, Simple, and Reproducible HPLC-ESI-Q-TOF MS Analysis and Their Antioxidant Activities. ACS Omega. 2022;7(16): 13475-13493, DOI: 10.1021/acsomega.1c06335.
70. Sacici E. (2017). Hgh performance thin-layer chromatographic method applications for qualitative and quantitative analysis of flowering aerial parts of hypericum perforatum L. and their implementations for some hypericum species and products. [Doctoral thesis, Yeditepe University].
71. Gioti EM, Fiamegos YC, Skalkos DC, Stalikas CD. Antioxidant activity and bioactive components of the aerial parts of Hypericum perforatum L. from Epirus, Greece. Food Chem. 2009;117:398-404. https://doi.org/10.1016/j.foodchem.2009.04.016.
72. Meinke MC, Schanzer S, Haag SF, Casetti F, Müller ML, Wölfle U, Kleemann A, Lademann J, Schempp CM. In vivo photoprotective and anti-inflammatory effect of hyperforin is associated with high antioxidant activity in vitro and ex vivo. Eur J Pharm Biopharm. 2012 Jun;81(2):346-50. doi: 10.1016/j.ejpb.2012.03.002.
73. Haag SF, Tscherch K, Arndt S, Kleemann A, Gersonde I, Lademann J, Rohn S, Meinke MC. Enhancement of skin radical scavenging activity and stratum corneum

lipids after the application of a hyperforin-rich cream. Eur J Pharm Biopharm. 2014 Feb;86(2):227-33. doi: 10.1016/j.ejpb.2013.06.016.
74. Saad B. Prevention and Treatment of Obesity-Related Inflammatory Diseases by Edible and Medicinal Plants and Their Active Compounds. Immuno. 2022;2:609–629. https://doi.org/ 10.3390/immuno2040038.